(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 175 917 A1

# (12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
**30.01.2002 Bulletin 2002/05**

(51) Int Cl.[7]: **A61M 1/34**, A61M 1/16

(21) Application number: **00114654.7**

(22) Date of filing: **07.07.2000**

(84) Designated Contracting States:
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE**
Designated Extension States:
**AL LT LV MK RO SI**

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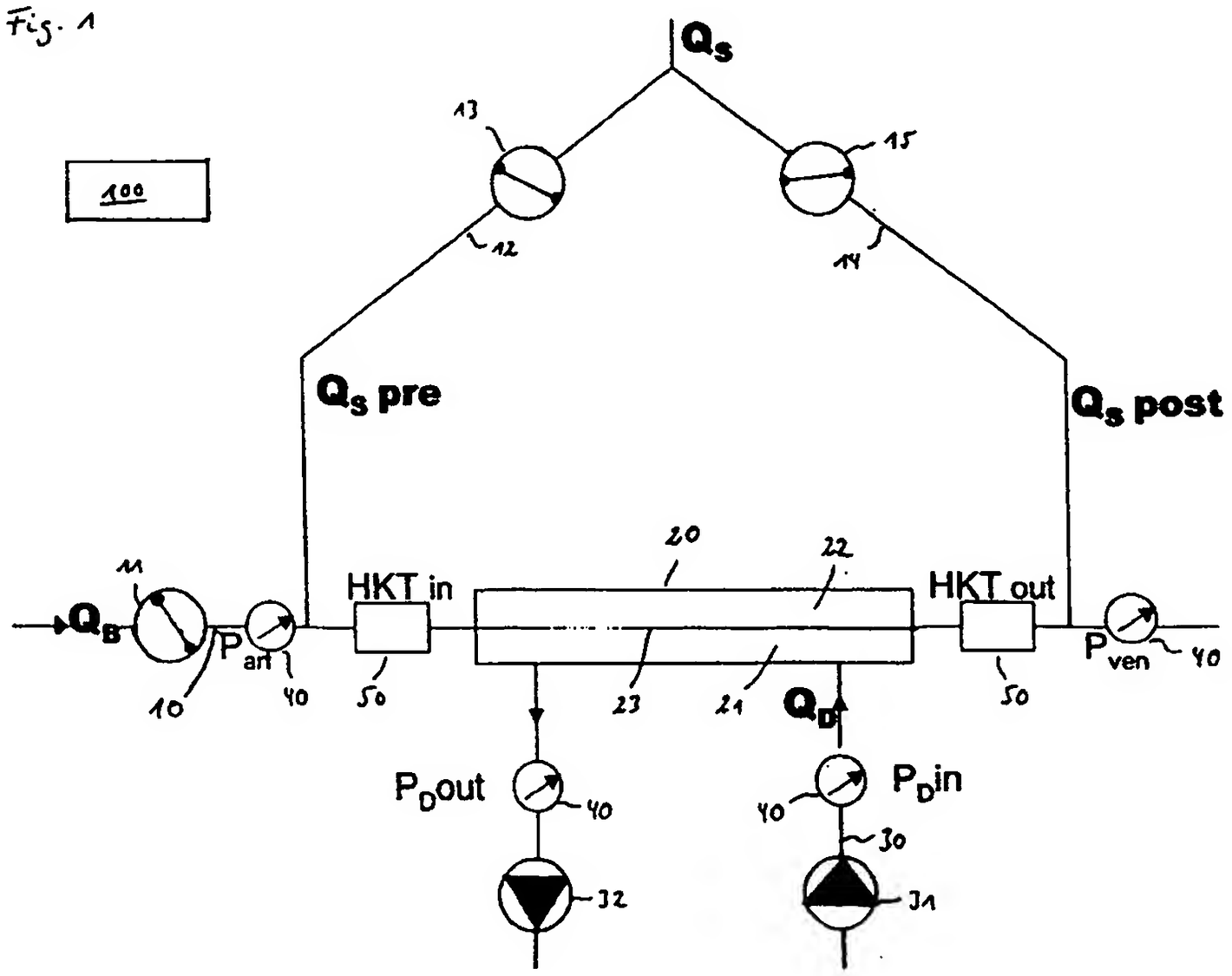
## (54) Hemodialysis method and apparatus

(57) The present invention refers to a method for blood purification by means of hemodialysis and/or hemofiltration, wherein to the blood in the extra-corporeal circuit (10) of the hemodialysis and/or hemofiltration device (20) a substitution solution is added upstream as well as downstream of the hemodialyser and/or hemofilter (20). A purification effect remaining constant with a high purification performance is achieved in that one or several of the operational and/or blood parameters are controlled and that the control is carried out using at least one of the infusion rates of the substitution solutions supplied upstream or downstream of the hemodialyser and/or hemofilter. The present invention also refers to a hemodialysis and/or hemofiltration apparatus for the performance of the inventive method.

Fig. 1

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## Description

**[0001]** The present invention refers to a method for blood purification by means of hemodialysis and/or hemofiltration, wherein to the blood in the extra-corporeal circuit of the hemodialysis and/or hemofiltration device a substitution solution is added upstream as well as downstream of the hemodialyser and/or hemofilter.

**[0002]** In "Replacement of Renal Function by Dialysis" (Drukker, Parsons and Maher; Kluwer Academic Publishers, 4th edition 1996; "Hemodialysis Machines and Monitors" by H.-D. Polaschegg and N. W. Levin) - to the disclosure of which is explicitly referred hereby - a summary of most important hemodialysis procedures and machines is given:

**[0003]** In hemodialysis the blood of a patient is fed through an arterial blood line into the blood chamber of a dialyser. The blood is usually transported by means of a rotary peristalic pump arranged in the arterial blood line. After passing the pump blood is fed through the blood chamber of the dialyser and finally through a venous drip chamber and a venous blood line connected thereto back to the patient. A venous pressure monitor is connected to the venous drip chamber as a protective system for immediate detection of blood loss to the environment. If necessary two needles required for the arterial and venous cannula may be replaced by a single needle in the so-called single-needle-dialysis. In this mode of dialysis, the extra-corporal circuit consists of a single needle cannula with connected Y-piece. From the dialyser the venous line leads back to the Y-piece. The arterial and venous line are occluded alternately by clamps. One or more blood pumps run to manage the alternate flow to and from the Y-piece.

**[0004]** In hemodialysis the solute removal from the blood is driven by diffusion through the dialyser membrane. Though in addition a small transmembrane pressure is applied in order to ultrafiltrate excessive water of a patient, this filtration hardly plays a role for the purification of the blood from specific substances.

**[0005]** Solute removal in hemofiltration is driven by convection rather than by diffusion. At the same time ultrafiltrate is almost entirely replaced by a substitution fluid of a composition similar to dialysate in dialysis. This method emphasizes the similarity to the natural kidney and the more effective removal of larger molecules. On the other hand removal of low molecular substances is reduced as compared to hemodialysis because at best 45% of blood can be ultrafiltrated in the so-called post-dilution hemofiltration. Today, hemofiltration is only used in a small number of patients because of the high cost of commercial replacement fluid and the high blood flow required to perform the treatment in a reasonable time.

**[0006]** Hemofiltration machines for chronic treatment comprise the same extracorporal pumping and monitoring systems as hemodialysis machines. The dialysate circuit is replaced by a fluid balancing and warming system. In the so-called pre-dilution mode substitution fluid is added to blood upstream of the dialyser and the filtrate is produced by the corresponding transmembrane pressure. To be clinically effective a very large amount of substitution fluid is required. Because of the high cost of commercial substitution fluid this method never became widely accepted. More common is the post-dilution mode because less substitution fluid is required. In this mode the substitution fluid is added to the blood downstream of a dialyser. In the post-dilution mode good purification coefficients are obtained. During a 4 hour treatment normally approximately 20 to 24 liters of substitution fluid are added. The efficiency of the method is, however, limited by a critical transmembrane pressure above which blood damage will occur.

**[0007]** Various systems have been proposed for fluid balancing. In the gravimetric balancing method ultrafiltrate may be withdrawn by the ultrafiltrate pump into a bag or container hanging or standing on a balancing platform. Substitution fluid from a bag or container on the same platform is pumped by another pump to the venous drip chamber. Net fluid removal is achieved either by an additional ultrafiltration pump or by a programming unit that controls the substitution pump to deliver less fluid than removed by the filtration pump.

**[0008]** Hemodiafiltration, a combination of hemodialysis and hemofiltration, can be performed by combining the extracorporal circuits of a hemofiltration and a hemodialysis machine. Hemodialysis machines with volumetrically controlled ultrafiltration can be adapted easily for hemodiafiltration which is more cost-effective. This is particularly cost-effective if the substitution fluid is prepared online from the dialysis fluid.

**[0009]** Treatment parameters such as dialysate contents (sodium concentration), ultrafiltration rate, blood and dialysate flow are varied intradialytically in an attempt to increase or maintain efficacy and/or reduce intradialytic symtoms. The variation either follows a kinetic model or, more often, "clinical judgement". Intradialytic symptoms, especially hypotension, are closely related to ultrafiltration. In dialysis machines having ultrafiltration pumps independent of dialysate pumps, profiling is performed by variation of the ultrafiltration speed.

**[0010]** To summarize in hemodialysis the blood of the patient is purified in that the substances of the blood which have to be removed diffuse through the membrane due to a concentration gradient across the membrane of the dialyser and thereby reach the dialysis fluid. The driving force in hemofiltration is substantially a pressure difference across the membrane which effects a convective transport of substances through the membrane and in doing so cleans the blood above all also from higher-molecular substances. In hemofiltration as well as in the combined method of hemodiafiltration, fluid is removed from the patient blood which has to be substituted except a small difference amount for the control of the fluid balance.

**[0011]** The relatively low efficiency of the pre-dilution mode, especially for low-molecular substances, results

from the low concentration gradient across the membrane caused by the dilution and the fact that a purification of the blood as well as of the added substitution liquid is carried out. For the pre-dilution mode, the amounts of substitution fluid added during a 4 hour treatment lie in a range between 40 to 50 liters.

**[0012]** Pre-dilution is used preferably for patients who have a higher risk of coagulation or clotting of the blood. Said risk is reduced by the dilution of the blood prior to blood treatment wherein the cited disadvantages are accepted.

**[0013]** As mentioned above disadvantages occur in post-dilution as it has to be worked with high hemoconcentrations. With respect thereto the hemoconcentrations in pre-dilution are low at least in the entrance section of the hemodialyser and/or hemofilter. Low hematocrit concentrations result in correspondingly large amounts of free water, i.e. unbound water, which renders possible a distinct convective substance transport through the membrane. Correspondingly, the purification effect for middle- and high-molecular substances may be higher in the pre-dilution mode than in the post-dilution mode.

**[0014]** To couple the advantages of the pre- and post-dilution mode it has also been proposed to apply both modes simultaneously with a fixed ratio of pre- and post-dilution substitution fluid flow (L. Pedrini and V. De Cristofaro, Abstract at the EDTA/ERA Congress in Madrid, 1999).

**[0015]** A further disadvantage of the post-dilution mode is that during the blood purification a limiting membrane is built up at the membrane of the hemodialyser and/or hemofilter. The thickness of this membrane increases with increasing duration of treatment, which reduces the permeability of the membrane. Thereby - if the trans-membrane pressure remains constant - the purification effect is deteriorated. If a constant purification effect was to be achieved, an increasing trans-membrane pressure would be required which can lead to a damaging of the membrane.

**[0016]** U.S. Patent 5,578,223 discloses an artificial kidney working in the post-dilution mode and being adaptable for use in hemofiltration, hemodialysis and hemodiafiltration treatment. For maintaining a desired concentration of bicarbonate in the blood of a patient the apparatus comprises means for perfusing a liquid containing bicarbonate into the extracorporal blood circuit after passing the exchanger and dosage means for adjusting the bicarbonate concentration in the blood of a patient to a desired level. An extraction pump which is connected to the outlet of the exchanger is controlled by a control unit to obtain a desired level of weight loss during the treatment session. The flow rate of bicarbonate solution is controlled by the control unit as a function of the flow rate of the extraction pump, the desired bicarbonate concentration in the blood of a patient and of the concentration of the bicarbonate solution before perfusion into the extracorporal circuit.

**[0017]** It is the object of the present invention to provide a method for the blood purification by means of hemodialysis and/or hemofiltration by means of which the advantages of the post-dilution mode and pre-dilution mode can be combined and at the same time the purification effect of the hemodialyser and/or hemofilter remains constant.

**[0018]** Proceeding from a method of the generic type, said object is solved in that one or several of the operational and/or blood parameters are controlled and that the control is carried out using at least one of the infusion rates of the substitution solutions supplied upstream or downstream of the hemodialyser and/or hemofilter.

**[0019]** By adding substitution solutions to the extracorporeal circuit upstream and downstream of the hemodialyser and/or hemofilter, on the one hand the advantages of the post-dilution and pre-dilution can be combined, i.e. satisfying purification results are obtained for low-molecular substances as well as for middle- and high-molecular substances. On the other hand, according to the invention the infusion rates of one or both of the substitution fluids supplied upstream and downstream are used for the control of operational and/or blood parameters.

**[0020]** Thus, for instance in case of a high trans-membrane pressure or a high hematocrit value of the blood, the infusion rate of the substitution solution added upstream of the dialyser can be increased until the desired values for the values to be controlled are achieved or the values fall below given limiting values. Correspondingly, in case of a low trans-membrane pressure or a low hematocrit value, the infusion rate of the substitution fluid supplied downstream of the dialyser can be increased which, due to the then resulting larger concentration gradient across the membrane leads to an improvement of the diffusive substance transport, i.e. to an improved purification effect for low-molecular substances.

**[0021]** According to a preferred embodiment of the present invention the operational and/or blood parameters are the trans-membrane pressure and/or the blood density and/or the hematocrit value of the blood.

**[0022]** The infusion rate of the substitution solutions supplied upstream of the hemodialyser and/or the hemofilter is preferably increased relative to the infusion rate supplied downstream of the hemodialyser and/or the hemofilter with increasing trans-membrane pressure and/or increasing blood density and/or increasing hematocrit value of the blood.

**[0023]** According to a preferred embodiment of the present invention the operational and/or blood parameters are detected continuously.

**[0024]** It is particularly advantageous when the infusion rates of the substitution solutions are chosen such that a substantially stationary limiting membrane is formed on the side of the membrane of the hemodialyser and/or hemofilter facing the chamber through which the blood flows. Therefrom results the advantage that the efficiency and the sieving-coefficient spectrum of the he-

modialyser and/or hemofilter remain constant during the time of treatment.

**[0025]** In a further embodiment of the present invention the relation of the infusion rates of the substitution solutions in the blood stream is changed after termination of the treatment in order to dissolve the limiting membrane. Thereby a major part of the proteins forming the limiting membrane can be supplied back to the patient after finishing the blood treatment.

**[0026]** The present invention also refers to a hemodialysis and/or hemofiltration apparatus with an extra-corporeal circuit for receiving the blood to be purified as well as with a hemodialyser and/or hemofilter communicating with the blood circuit, wherein, upstream and downstream of the hemodialyser and/or hemofilter, the blood circuit has at least one supply line, respectively, for supplying substitution fluid. According to the invention, a control unit for controlling one or several operational and/or blood parameters is provided, wherein the control unit is designed such that the control is carried out by means of at least one of the infusion rates of the substitution solution.

**[0027]** In a preferred embodiment of the present invention measuring devices connected to the control unit are provided for recording the operational and/or blood parameters. Therein said measuring devices can comprise pressure sensors arranged in the extra-corporeal circuit and/or in the dialysis-fluid circuit upstream and/or downstream of the hemodialyser and/or hemofilter, respectively.

**[0028]** In a further embodiment of the present invention the measuring devices comprise sensors in the extra-corporeal circuit upstream and/or downstream of the hemodialyser and/or hemofilter for the detection of the hematocrit value.

**[0029]** According to a preferred embodiment means for controlling the at least one of the infusion rates ($Q_s$pre, $Q_s$post) are pumps in the supply lines.

**[0030]** In a further embodiment means for controlling the at least one of the infusion rates ($Q_s$pre, $Q_s$post) are valves in the supply lines.

**[0031]** Further details and advantages of the present invention will be explained by means of an embodiment represented in detail in the drawing, wherein

**[0032]** Fig. 1 is a schematic representation of a part of the extra-corporeal circuit as well as of the dialysis fluid circuit with hemodialyser and hemofilter as well as supply lines for the substitution fluid.

**[0033]** Fig. 1 shows a part of the extra-corporeal circuit 10 through which blood is circulated with the flow rate $Q_B$ in the direction of the arrow by a blood pump 11. In the extra-corporeal circuit 10, upstream of the hemodialyser or hemofilter 20, there is arranged a pressure sensor 40 as well as a sensor 50 for the detection of the arterial blood pressure $p_{art}$ as well as of the hematocrit value $HKT_{in}$ prior to the blood purification.

**[0034]** Downstream of the hemodialyser and/or hemofilter 20 there are arranged corresponding measuring devices 40, 50 for the detection of the corresponding values $p_{ven}$ and $HKT_{out}$ after the blood purification.

**[0035]** In the counterflow to the blood flow, dialysis fluid flows through the hemodialyser or hemofilter 20 with the flow rate $Q_D$ in the direction of the arrow. The dialysis fluid line 30 has pressure sensors 40 upstream as well as downstream of the hemodialyser or hemofilter for the respective pressure $p_D$in and $p_D$out of the dialysis fluid. The circulation of the dialysis fluid is controlled by pump and/or balancing means 31 and 32.

**[0036]** The hemodialyser and/or hemofilter is divided by a semi-permeable membrane 21 into a blood chamber 22 and a dialysis fluid chamber 23.

**[0037]** Upstream and downstream of the hemodialyser or hemofilter 20 there are provided supply lines 12, 14, with fluid pumps 13, 15 respectively, by means of which substitution fluid is supplied to the blood flowing in the extra-corporeal circuit 10 during the treatment. The respective flow rates are characterized with $Q_s$pre and $Q_s$post.

**[0038]** Both infusion rates $Q_s$pre and $Q_s$post of the substitution fluid can be varied according to the invention by means of a control unit 100. The control unit 100 is connected to all shown actuators and sensors by not shown connections. The variation of the infusion rates is carried out in accordance with the measuring values of the control values to be controlled. According to the embodiment shown in figure 1 the measuring values are the arterial and venous blood pressure $p_{art}$, $p_{ven}$ as well as the pressure of the dialysis fluid $p_D$in and $p_D$out prior to and after passing the hemodialyser and hemofilter 20. The trans-membrane pressure TMP determined therefrom is adjusted according to the invention by a suitable variation of the flow rates $Q_s$pre and $Q_s$post to the desired target value or is maintained at said value. Instead of the trans-membrane pressure TMP the hematocrit values $HKT_{in}$, $HKT_{out}$ may be used as control values. The TMP may also be approximated by less than the shown four pressure sensors. In current dialysis machines it is common to use pressure sensors only for $p_{ven}$ and $p_D$out.

**[0039]** By using the claimed method or the claimed apparatus it is achieved that the limiting membrane building up on the side of the membrane of the hemodialyser or hemofilter facing the chamber in which the blood is present can be kept in a stationary state which results in a constant purification spectrum as well as a constant degree of purification during the treatment. At the same time the trans-membrane pressure can be kept constant during the treatment, as the pressure loss caused by the membrane and the limiting membrane also remains constant.

**[0040]** By the limitation of the trans-membrane pressure to a predeterminable value the danger of an extensive loss of albumin through the membrane caused by large convective forces can be prevented. If high-flux membranes are used the limitation of the trans-membrane pressure is particularly important.

**[0041]** Especially for patients with strong coagulation problems the combination of pre- and post-dilution also helps to reduce the heparin consumption which is usually infused into the blood to avoid blood coagulation in the extra-corporal circuit. If the blood is diluted upstream the hemodialyser and/or hemofilter, less anti-coagulating fluid is required to reduce the danger of blood coagulation in the hemodialyser and/or hemofilter as the latter represents the most significant potential for blood coagulation in the extra-corporal blood circuit.

**[0042]** Apart from the above mentioned advantages of a constant operational behavior, by the combination of pre-dilution and post-dilution good purification performances for low-molecular as well as middle- and high-molecular substances can be obtained.

## Claims

1. A method for blood purification by means of hemodialysis and/or hemofiltration, wherein to the blood in the extra-corporeal circuit (10) of a hemodialysis and/or hemofiltration device a substitution solution is added upstream as well as downstream of the hemodialyser and/or hemofilter (20),
   **characterized in**
   **that** one or several of the operational and/or blood parameters are controlled and that the control is carried out using at least one of the infusion rates ($Q_s$pre, $Q_s$post) of the substitution solutions supplied upstream or downstream of the hemodialyser and/or hemofilter (20).

2. The method according to claim 1, **characterized in that** the operational and/or blood parameters are the trans-membrane pressure (TMP) and/or the blood density and/or the hematocrit value (HKT) of the blood.

3. The method according to claim 1 or 2, **characterized in that** the infusion rate ($Q_s$pre) of the substitution solution supplied upstream of the hemodialyser and/or the hemofilter (20) is preferably increased relative to the infusion rate ($Q_s$post) supplied downstream of the hemodialyser and/or the hemofilter with increasing trans-membrane pressure (TMP) and/or increasing blood density and/or increasing hematocrit value (HKT) of the blood.

4. The method according to one or several of claims 1 through 3, **characterized in that** the operational and/or blood parameters are detected and controlled continuously.

5. The method according to one or several of claims 1 through 4, **characterized in that** the infusion rates ($Q_s$pre, $Q_s$post) of the substitution solutions are chosen such that a substantially stationary limiting membrane is formed on the side of the membrane of the hemodialyser and/or hemofilter (20) facing the chamber through which the blood flows.

6. The method according to claim 5, **characterized in that** after termination of the treatment the limiting membrane is dissolved by changing the relation of the infusion rates ($Q_s$pre, $Q_s$post) of the substitution solutions in the blood stream.

7. A hemodialysis and/or hemofiltration apparatus with an extra-corporeal circuit (10) for receiving blood to be purified as well as with a hemodialyser and/or hemofilter (20) communicating with the blood circuit (10), wherein upstream and downstream of the hemodialyser and/or hemofilter (20) the blood circuit (10) has at least one supply line (12, 14), respectively, for supplying a substitution fluid,
   **characterized in**
   **that** a control unit (100) for controlling one or several operational and/or blood parameters is provided, wherein the control unit is designed such that the control is carried out by means (13, 15) of at least one of the infusion rates ($Q_s$pre, $Q_s$post) of the substitution solution.

8. The hemodialysis and/or hemofiltration apparatus according to claim 7, characterized in that measuring devices are connected to the control unit for recording the operational and/or blood parameters.

9. The hemodialysis and/or hemofiltration apparatus according to claim 8, characterized in that said measuring devices comprise pressure sensors (40) arranged in the extra-corporeal circuit (10) and/or in the dialysis-fluid circuit (30) upstream and/or downstream of the hemodialyser and/or hemofilter (20), respectively.

10. The hemodialysis and/or hemofiltration apparatus according to claim 8 or 9, **characterized in that** the measuring devices comprise sensors (50) arranged in the extra-corporeal circuit (10) upstream and/or downstream of the hemodialyser and/or hemofilter (20) for the detection of the hematocrit value (HKT) of the blood.

11. The hemodialysis and/or hemofiltration apparatus according to one of claims 7 to 11 **characterized in that** the means for controlling the at least one of the infusion rates ($Q_s$pre, $Q_s$post) are pumps (13, 15) in the supply lines (12, 14).

12. The hemodialysis and/or hemofiltration apparatus according to one of claims 7 to 11 charactrized in that the means for controlling the at least one of the infusion rates ($Q_s$pre, $Q_s$post) are valves in the sup-

ply lines (12, 14).

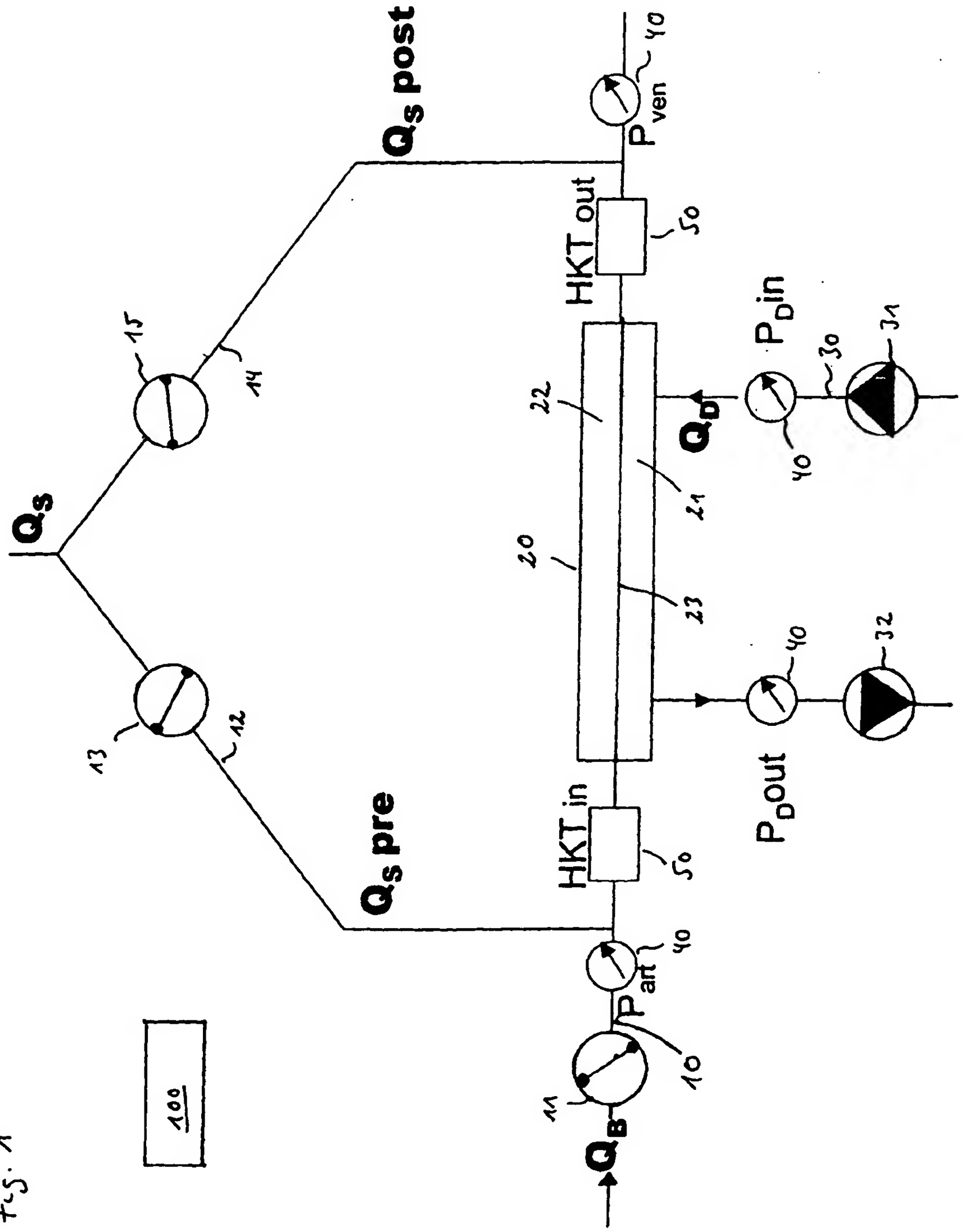
$Q_S$ post
$P_{ven}$
40
HKT out
50
15
14
$Q_S$
22
$Q_D$
$P_{Din}$
30
31
40
20
21
23
13
12
$Q_S$ pre
HKT in
50
$P_{Dout}$
40
32
$P_{art}$
40
11
10
$Q_B$
100

Fig. 1

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# PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 00 11 4654

## DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.7) |
|---|---|---|---|
| X<br>Y | WO 98 50091 A (DROZ CLAUDE ;FAVRE OLIVIER (CH)) 12 November 1998 (1998-11-12)<br>* page 10, line 16 - page 12, line 17; figure 1 *<br>--- | 7-9,11,<br>12<br>10 | A61M1/34<br>A61M1/16 |
| X | WO 00 09182 A (KAHN JEAN MAURICE ;ALPAMED S A (CH); JUNOD MICHEL (CH); LEVEQUE ER) 24 February 2000 (2000-02-24)<br>* page 5, line 9 - page 8, line 25; figures 1-6 *<br>--- | 7 | |
| X | DE 42 40 681 A (FRESENIUS AG)<br>9 June 1994 (1994-06-09)<br>* column 4, line 30 - column 5, line 50; figures 1,3 *<br>* column 8, line 40 - column 9, line 17 *<br>--- | 7 | |
| Y | EP 0 358 873 A (FRESENIUS AG)<br>21 March 1990 (1990-03-21)<br>* page 3, line 40 - line 50; figure 1 *<br>* page 4, line 30 - line 56 *<br>--- | 10 | |

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

A61M

## INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

1-6

Reason for the limitation of the search:

Article 52 (4) EPC - Method for treatment of the human or animal body by surgery
Article 52 (4) EPC - Method for treatment of the human or animal body by therapy

| Place of search | Date of completion of the search | Examiner |
|---|---|---|
| THE HAGUE | 2 October 2000 | Zeinstra, H |

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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L : document cited for other reasons

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EPO FORM 1503 03.82 (P04C07)

## ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 11 4654

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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02-10-2000

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 9850091 A | 12-11-1998 | AU 6849998 A | 27-11-1998 |
| | | EP 0980275 A | 23-02-2000 |
| WO 0009182 A | 24-02-2000 | NONE | |
| DE 4240681 A | 09-06-1994 | NONE | |
| EP 0358873 A | 21-03-1990 | DE 3827553 C | 26-10-1989 |
| | | AT 106756 T | 15-06-1994 |
| | | DE 58907818 D | 14-07-1994 |
| | | ES 2057028 T | 16-10-1994 |
| | | JP 2211173 A | 22-08-1990 |
| | | JP 2869735 B | 10-03-1999 |
| | | US 5230341 A | 27-07-1993 |

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82